International Journal of Neuroscience, 119:1–14, 2009
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ISSN: 0020-7454 / 1543-5245 online
DOI: 10.1080/00207450802480283

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PRENATAL EXPOSURES TO LTP-PATTERNED MAGNETIC FIELDS: QUANTITATIVE EFFECTS ON SPECIFIC LIMBIC STRUCTURES AND ACQUISITION OF CONTEXTUALLY CONDITIONED FEAR

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Weak (<1 μT) complex magnetic fields (CMFs) may exert their behavioral influences through the hippocampus by resonating by accident or design with intrinsic electrical patterns. Rats were exposed prenatally to one of four intensities of a CMF (either <5 nanoTesla [nT], 10–50 nT, 50–500 nT, or 500–1000 nT) designed to interact with the process of Long-Term Potentiation (LTP) in the hippocampus. Rats then underwent testing in the forced swim, open field, and fear-conditioning procedures. The cell densities of all amygdaloid nuclei, specific hypothalamic structures, and the major regions of the hippocampus were quantified. Results showed that acquisition of conditioned fear was strongly inhibited in animals exposed to LTP-CMFs. Rats exposed to intensities above 10 nT showed decreased cell density in the CA2 fields of the hippocampus; more neurons were present in the CA1 fields of rats exposed to the 10–50 nT intensities compared to all other groups. A decrease in cell density in the medial preoptic nucleus was linearly dependent on field intensity. In the forced-swim test, swimming was decreased in rats that had been exposed to low (10–50 nT) and medium intensity (50–500 nT) LTP-CMFs in a manner consistent with monoamine modulation. In the open field, exposed rats were indistinguishable from controls. These findings support the hypothesis that continuous exposure during prenatal development to CMFs designed to simulate intrinsic LTP within the hippocampus can affect adult behaviors specific to this structure and produce quantitative alterations in neuronal density.

Keywords conditioned fear, hippocampus, Long-Term Potentiation, rat

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INTRODUCTION

Application of weak intensity-varying and temporally complex magnetic fields (CMFs) produces a wide spectrum of behavioral sequelae in organisms from *Rattus norvegicus* to *Homo sapien* (Persinger, Ludwig, & Ossenkopp, 1973; Sienkiewicz, Jones, & Bottomley, 2005). Alterations in the neuronal organization of limbic structures, which might underlie these behavioral changes, may also result from CMF exposure. Such effects are most probable when the organism is exposed during the prenatal or perinatal period and when the nervous system is undergoing rapid development and is vulnerable even to subtle stimuli (Auroux, 1997).

Perinatal exposure to 0.5 Hz rotating magnetic fields within the milliTesla range has been shown to reduce cell density in the medial preoptic nucleus in male but not female rats (Persinger & Mulligan, 2001). Weaker (nanoTesla range) 0.5 Hz square-wave CMFs with hourly alterations in amplitude

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influenced the cell density of the parasolitary nucleus (Dupont, McKay, Parker, & Persinger, 2004) while CMF within the 10 nT to 50 nT range dramatically changed hippocampal cell morphology (St-Pierre & Persinger, 2003). In each of these experiments, a distinct CMF was applied that modeled a natural biological or environmental time-varying pattern. Field intensities were very weak, i.e., within the nanoTesla to microTesla range.

Complex magnetic fields, which have asymmetrical and irregular time-varying patterns, may be more potent than the sine or square waveforms popularly employed in laboratory settings (Martin, Koren, & Persinger, 2004). While the property of differential sensitivity to the time-varying patterns of magnetic fields has been known for decades (Adey, 1981), the exact reason for this is unknown. One possibility might be the "physiological relevance" of the waveform (McKay, Koren, & Persinger, 2003a; McKay, St-Pierre, & Persinger, 2003b). Data suggest that CMFs modeled after naturally occurring time-varying processes may be more effective because they are biologically relevant (Persinger, 2006).

In support of this assumption, CMFs whose temporal structure was modeled after the burst firing of amygdaloid neurons elevated nociceptive thresholds in rats (Ryczko & Persinger, 2002; Martin et al., 2004) and reduced psychometric depression in humans (Baker-Price & Persinger, 1996; 2003). In addition, CMFs modeled after theta burst-firing neurons in the hippocampus, a pattern of activity that can induce LTP in hippocampal slices (Rose, Diamond, Pang, & Dunwiddie, 1988), have powerful effects on learning. Depending upon the exact timing used, LTP-CMF can interfere with the acquisition of the conditioned fear response (Stewart & Persinger, 1999; McKay, Persinger, & Koren, 2000) or enhance learning in the radial arm maze (McKay et al., 2003b). CMFs modeled after the activity patterns of limbic structures have the potential to influence a variety of states even at these weak (<microTesla) intensities. In contrast, prenatally applied symmetrical (50 Hz) waveforms with intensities thousands of times greater do not generate behavioral changes (Sienkiewicz, Robbins, Haylock, & Saunders, 1994).

While the effects of LTP-CMF on behavior are robust (with the treatment ranging between 20% and 75% of the variance in the dependent variable), quantitative data for their neuroanatomical correlates have not been examined until recently. In many cases the attribution of cause is speculative. Behavioral testing accompanied by a detailed neurohistological examination could shed light on the mechanisms by which LTP-CMF affect behavior. Knowing the "susceptible" structures might facilitate the development of magnetic field-based therapies (Liboff, 2004).

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We reasoned that a series of experiments in which the behavioral and histological consequences of prenatal exposures to a specifically designed LTP-CMF were examined systematically might reveal specific brain-behavior associations. Because LTP-CMF patterns have influenced behaviors in a manner consistent with alterations of hippocampal structures (Stewart & Persinger, 1999; McKay et al., 2000; Delparte & Persinger, 2007), and the limbic system in general appears to be sensitive to magnetic fields, we concentrated upon the nuclear regions within the hippocampus, amygdala, and hypothalamus. If indeed long-term behavioral changes are induced by prenatal or perinatal exposure to these LTP-CMF patterns, corresponding neuronal changes should be found.

MATERIAL AND METHODS

Subjects

In Experiment 1, 16 male 90-day-old Wistar albino rats were randomly selected from the litters of eight pregnant dams that had each been exposed to one of the four different intensities of the LTP-CMF as described below. In Experiment 2, a total of 34, 90-day-old male and female rat pups were randomly selected from another set of litters generated from eight pregnant dams exposed to the treatment. There were two litters per each of the four intensity groups. In addition, 15 age-matched controls not exposed to any magnetic field treatment were selected. In Experiment 3, ten 90-day-old male rats were employed. Six had been exposed to the LTP-CMF intensities and four were controls.

Magnetic Field Exposures

As described previously (St-Pierre & Persinger, 2003), pregnant females were housed in one of the four adjacent plastic chambers that were placed between two magnetic coils. The intensities within each chamber were (1) very low (<5 nT), (2) low (10 to 50 nT), (3) medium (50 to 500 nT), and (4) high (500 nT to 1 mT). We assumed that very low intensity (<5 nT) exposure would be below the threshold required to produce effects discernable by our measurements. The fields were generated by converting a series of numbers by computer software to voltages that were all positive polarity through a digital-to-analogue converter.

All mothers in these studies had been impregnated in and exposed continuously to the LTP-CMF during their entire pregnancy. Litters were removed from the LTP-CMF exposure cages 1 or 2 days after birth and placed

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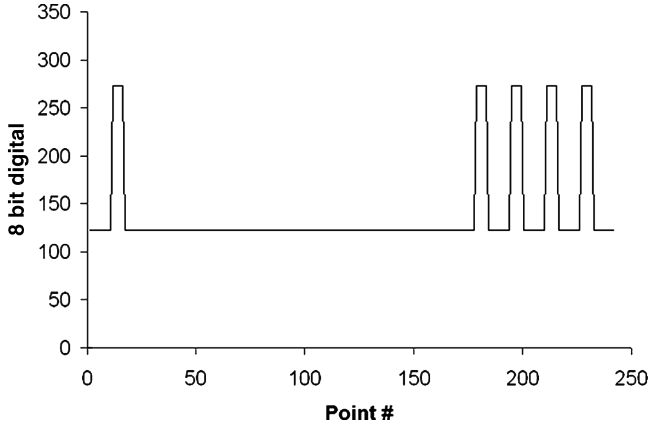

Figure 1. Time-varying pattern of one LTP pulse. Point duration is equivalent to 1 ms. Each 8-bit digital value is converted into a corresponding voltage.

in standard plastic rearing cages with their mothers until they were 21 days old. After that time the subjects were housed three per cage within standard wire cages.

The LTP-CMF (Figure 1) was designed to simulate the minimal pattern (Rose et al., 1988) that produced LTP in hippocampal slices. Throughout exposure, a complete cycle of the LTP-CMF included 10 s of continuous repetition of this pattern followed by 40 s of no field pattern (interstimulus interval). During the 10 s periods, when the field was activated, there were 50 successive (continuous) presentations of a 5 ms pulse followed 150 ms later by three successive 5 ms pulses each separated by 10 ms (equivalent of 100 Hz). The base duration of this "LTP" pulse was 200 ms (5 Hz).

Experiment 1: Forced-Swim Test and Histology

The rats were exposed to forced swimming for 15 min/day, for every second day for four consecutive weeks. A vertical cylinder (105-cm high, 45-cm diameter) was employed for the test; it contained 75 cm of water maintained at 25°C. Three categories of behaviors were measured: climbing, immobility, and swimming. The cylinder was divided into four quadrants. Swimming was defined as the number of times the rat traversed the border between quadrants. Climbing activity was defined as length of time (in seconds) the rat spent with the forepaws along the side of the cylinder while immobility was defined as time (in seconds) of inactivity.

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The brains of eight rats (littermates of those tested by forced swimming), two per intensity condition, were removed, fixed, and processed for histological examination. Within the boundaries of the telencephalon, 10-μm sections were taken every 100 μm and stained with toluidine blue O. At 400x magnification, the numbers of neurons within a 6 $\times$ 6 grid (.061 mm^2) from three separate samples were counted and averaged for various nuclei as designated by Paxinos and Watson (2004). The 12 amygdaloid nuclei (n.) areas were the central n., medial n., basomedial n., basolateral ventral n., basolateral n., lateral n., amygdalohippocampal area, posteromedial part, posterormedial cortical n., amygdalopiriform transition area, posterolateral cortical n., and anterior cortical n. The seven hypothalamic structures were the medial preoptic area and the six subdivisions of the paraventricular nucleus. The hippocampal regions were Cornu Ammonis (CA) fields 1 through 4 (hilar region) and the dentate gyrus. Numbers of neurons per unit area for each structure were transformed to z-scores for more obvious comparison between intensity levels.

Experiment 2: Open-Field Testing

Rats were individually tested for 2 min in an open-field box. It was 60-cm x 60-cm by 30-cm high. The floor was divided into 25 squares. During the observation period, the following measures were obtained: total squares traversed, episodes of rearing, episodes of grooming, numbers of fecal boluses, and deposits of urine. Following testing the animals were removed and weighed. Between trials the box was cleaned with 0.4% acetic acid and then dried.

Experiment 3: Fear-Conditioning Paradigm

The precise details of the fear-conditioning chamber have been described elsewhere (Stewart & Persinger, 1999). A rat was randomly selected and placed in the chamber for 3 min with no intervention to allow habituation. At the 3rd, 4th, and 5th min of the trial, the rat was administered a 0.5 mA shock for 2 s. The rat was observed for 6 min in total. This was termed training day. At the end of the trial, the animal was removed and the chamber was cleaned with 0.4% acetic acid. Approximately 24 hr later, the rat was returned to the chamber and observed for 8 min. This was termed the testing day. Every 8 s of this 8-min trial, the presence of movement was evaluated (either 0 = freezing or 1 = movement). As there are 60 intervals of 8 s within 8 min, the maximum total numbers of intervals with movement were therefore 60. Percentage freezing was calculated as

$$\text{Percentage Freezing} = ((60 - \text{Total Intervals with Movement})/60) \times 100.$$

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For the training day, time blocks of 1 min were used over the 6-min trial. These time blocks were: I_1 from 0–1 min, I_2 from 1–2 min, I_3 from 2–3 min, I_4 from 3–4 min, I_5 from 4–5 min, and I_6 from 5–6 min. On testing day, time blocks of 2 min were used over the 8-min trial. This generated four time intervals: T_1 from 0–2 min, T_2 from 2–4 min, T_3 from 4–6 min and T_4 from 6–8 min. Creation of these time blocks allowed for time-dependent analysis of the data.

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RESULTS

Experiment 1: Forced-Swim Test and Histology

The grand means (M) and standard deviations (SD) for the totals of each of the three measures were swimming: 217 ± 70 counts, climbing: 240 ±112 s, and immobility 535 ± 131 s. There were statistically significant differences between the amount of swimming for the rats that had been exposed prenatally to the various LTP-CMF intensities [$F(3,4) = 7.84$, $p < .05$; $\eta^2 = .85$]. *Post-hoc* analyses indicated that the rats exposed to the low (10 to 50 nT) and medium intensities (50 to 500 nT) swam significantly less relative to the rats that had been exposed to the high (>500 nT) and very low intensities (<5 nT). The difference in means was equivalent to 1.5 SD. There were no statistically significant differences between prenatal exposure intensities for the other two behavioral measures.

Statistically significant differences in cell density of the LTP-CMF groups were found only for the CA1 [$F = 275.33$, $p < .001$, $\eta^2 = .99$] and CA2 [$F = 10.57$, $I < .05$; $\eta^2 = .89$] fields of the hippocampus and for the medial preoptic area [$F = 7.18$, $p < .05$; $\eta^2 = .84$] of the hypothalamus. The mean and SD for the numbers of neurons per unit area in these structures were 62.3 ± 5.4, 43.0 ± 9.4, and 98.0 ± 21.0, respectively. *Post-hoc* analyses indicated that for the CA1 sector rats that had been exposed to the 10 to 50 nT had significantly more neurons ($z = 1.3$) than any other intensity ($zs = 0.3$ to -1.0). For the CA2 sector, exposure to any field intensity 10 nT or above decreased neuronal density [$z = 0$ to -0.8] compared to those exposed to <5 nT fields [$z = 1.4$].

For the medial preoptic area, a linear decrease in the numbers of neurons occurred as a function of intensity. Rats that had been exposed to the highest intensity had the least ($z = -1.5$) numbers of neurons compared to those exposed to the lowest intensity ($z = 1.0$). There were no statistically significant differences between rats exposed to the various intensities for neuronal densities within the paraventricular hypothalamic nuclei or for any of the amygdaloid nuclei.

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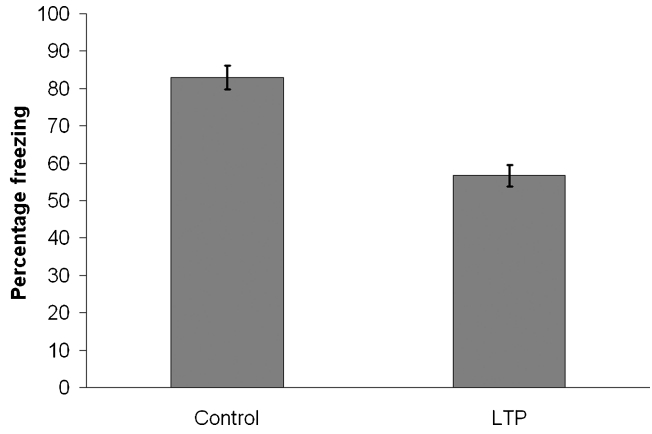

Figure 2. Mean and standard error of the mean for percentage freezing in rats given LTP-patterned magnetic field or no-CMF treatment.

Experiment 2: Open-Field Testing

One-way analysis of variance yielded no significant effects on any of the open-field behaviors measured at the sample size employed [all $F < 2$, n.s.]. The means and SDs for movement, grooming, rearing, defecation, and urination were 47.7 ± 23.7, 14.7 ± 4.8, 0.12 ± 2.7, 1.12 ± 1.81, and 0.57 ± 0.77, respectively.

Experiment 3: Fear-Conditioning Paradigm

Preliminary one-way analysis demonstrated no differences between the various intensities of LTP-CMF rats on any measures. However, p values approached significance and the effect size was great even though the sample size was small. An analysis was then reperformed grouping all LTP-CMF-treated rats together and comparing them to naïve controls. One-way analysis of variance by treatment group (either true control or LTP-CMF) showed a difference in movement on the testing day [$F(1,8) = 35.35$, $p < .01$, $\eta^2 = 0.82$] but not during the training day [$F = 0.23$, n.s.].

LTP-CMF rats moved significantly more often on the testing day ($M = 26.00$, $SD = 4.29$) than did the controls ($M = 10.25$, $SD = 3.77$). This increase in movement expressed as diminished freezing behavior is shown in Figure 2. *Post-hoc* analysis showed that movement was elevated during T_1, T_3, and T_4 time blocks but not during T_2 (Figure 3) time block.

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DISCUSSION

Acute exposures to LTP-CMF have been shown to impair associative learning in adult rats (Stewart & Persinger, 1999; McKay et al., 2000). Full-body exposures to this particularly patterned field in close temporal proximity to training sessions were employed. In the present study, prenatal exposures to LTP-CMF for a period of 22 days produced a long-term associative learning impairment, which was detectable at 90 days of age, 3 months after field treatment had stopped. The impairments shown were highly specific and accompanied by conspicuous alterations in cell densities within specific fields of the hippocampus. When not being tested on a contextual learning task, LTP-CMF-treated animals were indistinguishable from controls in the open-field test and performed very similarly to controls in the forced-swim test.

When placed in the chamber on the testing day, but not the training day, LTP-CMF rats demonstrated marked hyperactivity. These results are congruent with previous observations that show increased locomotion following shock in animals treated with magnetic fields (Stewart & Persinger, 1999). In addition, the pattern of movement of LTP-CMF rats on the testing day was abnormal. While control animals demonstrated uniformly low movement and high freezing across all time intervals, LTP-CMF-treated rats did not (Figure 3). In LTP-CMF rats, movement was elevated in all time blocks but T_2 (2–4 minutes). This time period corresponds to the administration of the first shock

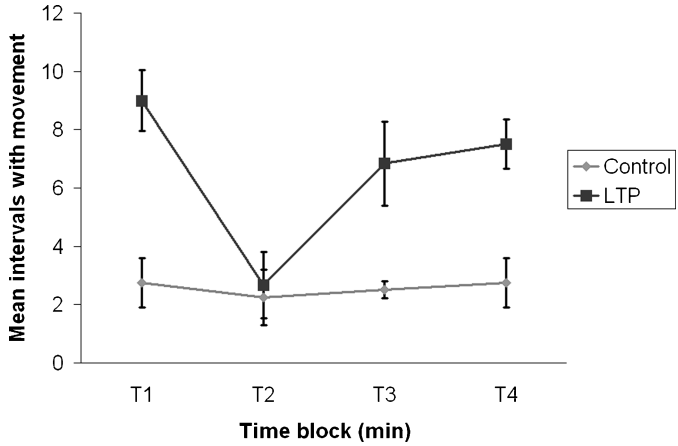

Figure 3. Mean number of intervals with movement by time block. $T_1 = 0$–2 min, $T_2 = 2$–4 min, $T_3 = 4$–6 min, $T_4 = 6$–8 min.

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on the training day (I_3 at 3 min). The failure to show freezing behavior in anticipation of the subsequent shocks (at I_4 and I_5) is difficult to explain. Effectively, only the first shock applied during the test day was "predicted" by the LTP-CMF rats, whereas the other shocks were not.

There were no statistically significant effects from prenatal exposures to the LTP intensities upon open-field behaviors. Normally, this measure is considered quite sensitive to magnetic field treatment (Whissell & Persinger, 2007b). On the other hand rats that had been exposed to the mid-level intensities (10 to 500 nT) showed less swimming behavior. While the decreased swimming behavior suggests a prodepressant effect of prenatal exposure to LTP-CMF, it is important to note that immobility, perhaps the best indicator of learned helplessness, did not differ between groups. We suggest that the prenatal exposures to LTP fields may have affected receptor as well as neuronal densities. Many magnetic field patterns affect these monoamines and their receptors (Whissell & Persinger, 2007a). Reduction in serotonin has been associated with reduction in movement in the forced-swim task (Cannizzaro et al., 2007) as has a reduction in dopamine (Clemens, Cornish, Li, Hunt, & McGregor, 2005).

That these deficits were caused by a finite period of exposure 3 months earlier suggested permanent changes in neurostructure had occurred. Histological examination of LTP-CMF rats showed intensity-dependent changes in cell density within the CA2 and CA1 hippocampal fields but no observable effects within the amygdala. As with many magnetic field studies, the direction of the effect, that is whether the cell density increased or decreased, differed within specific structures (Whissell & Persinger, 2007a). This sensitivity of a biological system to magnetic fields makes minute variations in field intensity a strong determinant of the direction of the effect.

The CA1 field is thought to play a critical role in contextual fear conditioning (Daumas, Halley, Frances, & Lassalle, 2005) and is also the primary output center of the hippocampus. Previously, it has been shown that experimental lesion to the dorsal hippocampus and its associated projection systems cause robust impairments in conditioned fear (Maren & Fanselow, 1997) and that these effects could be mimicked by application of LTP-patterned magnetic fields (Stewart & Persinger, 1999). The present study may be the "missing link" between the two, showing an inhibition of conditioned fear and accompanying alterations in neuronal density. It seems counterintuitive that brains with the highest cell density in the CA1 field would have the poorest performance. However, the organization of cells rather than absolute numbers may be the controlling factor. St-Pierre and Persinger (2003) observed a significant volume increase in the hippocampus of CMF-treated rats that was

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characterized by abnormal distribution of cells. This unusually high volume of cells may reflect an aberrant migration and lead to poor communication, and hence impaired function. While other experimental paradigms, which can include hypoxia as part of the treatment, show damage in the CA2 field and impaired conditioned fear (Fedorova, Jacobson, Basile, & Jacobson, 2003), additional damage is almost always noted elsewhere in the hippocampus in these cases and normally in CA1.

The contribution of cellular changes in the medial preoptic nucleus to differences in behaviors observed in these experiments is unclear. While it is known that the nucleus is indirectly involved in analgesic behavior (Hall & Behbehani, 1997) and magnetic fields have strong effects on analgesia (Shupak et al., 2006) through the opiate system (Whissell & Persinger, 2007a), the likelihood that long-term opiate changes occurred is low given that there were no differences in the baseline reactions on the training day in the fear-conditioning task.

Persinger and Mulligan (2001) showed that males but not females showed fewer neurons within the preoptic nucleus of the hypothalamus following perinatal exposures to 0.5 Hz magnetic fields of 0.1 mT or greater compared to sham-field controls. It is interesting that such reduction occurred here even with much weaker magnetic fields and that it was linearly proportional to the intensity. The physiological relevance of this waveform likely accounts for its greater penetrability at such a low strength. A nonspecific "feminization" of sexually dimorphic brain structures from environmental magnetic fields might be a possibility.

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ACKNOWLEDGEMENTS

The authors thank Dr. Robert Lafrenie and Dr. Glenn Parker for helpful comments and support. This work was partially supported by a grant from the Natural Sciences and Engineering Research Council of Canada (NSERC).

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